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January 6, 1994

Dr. Harmon C. McAllister
Associate Research Director
The Council for Tobacco Research
900 Third Avenue
New York, NY 10022

Dear Dr. McAllister:

I am writing this letter in order to request that you consider the possibility of providing funds through The Council for Tobacco Research to support the Conference on "Hepatic Regeneration and Carcinogenesis: Molecular and Cellular Pathways" to be held in Copper Mountain, Colorado, from August 7-12, 1994. This is an international conference organized by myself and Dr. Randy Jirtle (Duke University) and sponsored by the Federation of Associations for Experimental Biology (F.A.S.E.B.). Participants from USA, Western Europe and Japan have been invited and agreed to participate.

The rationale of the conference is the examination of the concepts relating to liver carcinogenesis based on recent discoveries of regulation (positive and negative) of growth of the normal hepatocyte by specific growth factors. Most of the classic concepts of carcinogenesis were originally developed by studies of liver carcinogenesis. The concept of "metabolic activation" of carcinogens and the demonstration of the role of microsomal cytochrome P450 in drug metabolism was derived from original studies in this area. Much of our understanding of tumor biochemistry came from studies of hepatocellular carcinomas. Given the capacity of the liver to regenerate, the mechanisms of liver regeneration were contrasted in the past to the mechanisms of carcinogenesis in pursuit of differences that would yield meaningful clues on the mechanisms of causation of neoplasia. Development of liver tumors is still the major endpoint for evaluation of carcinogenicity of chemicals (including new drugs and pharmaceuticals) by the NTP carcinogenesis bioassay.

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While the database on the phenomenology associated with liver carcinogenesis is large, little is known about the specific gene targets whose alterations of expression or structure are associated with hepatocarcinogenesis. In recent years, however, there has been a veritable explosion of information on the regulation of growth processes in normal and neoplastic liver. Growth factors (some of which are specific for the liver) have now been characterized while their receptors have been identified. Expression of specific cellular proto-oncogenes has been shown in relation to liver regeneration and carcinogenesis. Changes of growth factor receptors have been shown in relation to promotion of carcinogenesis in liver. The lineage of the specific cell types involved in hepatic carcinogenesis is now defined by specific enzymatic and immune markers. This has now become a very exciting area of investigation.

Participants to the conference have been invited from an international roster and they include scientists with national and international reputation for their work. Topics to be covered include models of multistage carcinogenesis, growth regulation of normal hepatocytes, interactions with extracellular matrix, growth inhibition of liver cells, role of proto-oncogenes and oncogenes in hepatocyte transformation, mechanisms of promotion and progression of carcinogenesis and cell lineages in hepatic carcinogenesis, etc.

I believe that support of this conference is to the interest of The Council for Tobacco Research. The research which will be brought together by the participants of this conference is bound to lead to discoveries of new molecules and processes for the regulation of normal and cancerous cell growth. Progress in this area should lead to rational development of new pharmaceutical agents for cell growth regulation. This conference should act as a catalyst for integration of information which should provide the intellectual basis for synthesis of new pharmaceuticals for control of cancerous growth. The impact of the information to be presented in this conference, however, transcends the boundaries of carcinogenesis. This information should also be of importance for development of new pharmaceuticals for control of hepatic disease. Growth of the normal hepatocyte is an integral part of any aspect of hepatic pathology. Regulation of this process should have major therapeutic impact on the control of fulminant hepatic failure (due mainly to failure of regeneration of hepatocytes), chronic active hepatitis (abnormal structure in the liver derived from continued regeneration in the face of altered micro-architecture) etc.

I recently submitted to NIH a proposal requesting support for this conference. This proposal is currently under review. This proposal describes the conference structure in all detail in terms of participants and their areas of expertise. We have, however, been told by NIH that although funding of the conference appears likely, the amount to be granted cannot exceed $6,000 and, depending on budgetary restrictions at NIH, could be substantially less. As we explain in the application, it would require approximately $50,000 to cover the traveling

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expenses and the registration fee for the invited participants. F.A.S.E.B. has pledged to give us $6,000. This leaves a gap of at least $38,000 which would be required to cover the expenses. The participants of this conference and myself would be grateful for any support that The Council for Tobacco Research could provide toward this end. I am making the request, based on the above, that The Council for Tobacco Research consider the possibility of contributing $5,000 toward support of this conference. If this is impossible, a contribution of any amount would be helpful.

Please let me know if any further information is required for consideration of my request.

Thank you for taking my request into consideration.

With best regards,

George K. Michalopoulos, M.D., Ph.D.
Professor and Chairman
Department of Pathology

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Enclosure: List of 1994 FASEB Summer Conferences

P.S. If a contribution is considered, checks should be annotated "Hepatic Regeneration" and made payable to: FASEB
9650 Rockville Pike
Bethesda, MD 20014

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